Original Article

Correlation Between Low Vitamin D Levels and Pre-eclampsia Onset in Late Pregnancy

Rubina Mustafa[1], Bushra Khan[2], Sadaf Zahra Syed[3], Muhammad Asim Iqbal Qureshi[4], Shermeen Kousar[5], Iqra Zafar[6]

[1]Woman Medical Officer, Obs & gynae Unit 1 LWH
[2]Associate Professor, Obstetrics and Gynaecology Deptt, Bakhtawar Amin Hospital, Multan
[3]Assistant Professor, Obs and Gynae Fatima Jinnah Medical university/SGRH unit 1
[4]Assistant Professor Obs Gynae, Bakhtawar Amin Medical College, Multan
[5]Senior Registrar, Gynae unit 1, Holy Family Hospital, Rawalpindi
[6]Consultant gynaecologist, Punjab Employees Social Security Institution, Lahore

Correspondence: Dr. Bushra khan
Associate Professor
Obstetrics and Gynaecology Deptt,
Bakhtawar Amin Hospital Multan
bushrakhandr@yahoo.com

Abstract

Objective: To explore the correlation between low vitamin D levels and the onset of pre-eclampsia in women presenting during third trimester of pregnancy.

Methodology: This study was conducted at department of Obstetrics and Gynaecology, Lady Willingdon Hospital (LWH), Lahore from June 2021 to 31 December 2021. All the women aged 18 years or older, gestational age more than 28 weeks, diagnosed with pre-eclampsia as per established clinical criteria were included. Equal numbers of normotensive women were selected as controls. A 5ml blood sample was collected from each participant to evaluate the vitamin D level. Vitamin D deficiency was defined as serum levels below 20 ng/mL All the information regarding data was collected using study proforma and SPSS version 26 was used for the data analysis.

Results: The average age for the case group was 27.22 ± 3.18 years, and for the control group, it was 26.31 ± 4.17 years. Similarly, the mean gestational age for the case group was 32.38 ± 3.5 weeks, and for the control group, it was 33.29 ± 2.7 weeks, with a significant p-value > 0.05. In the case group, 47 individuals (28.5%) were found to have hypovitaminosis D, while in the control group, 25 individuals (15.2%) were identified with the condition. The odds ratio (OR) 2.23 (95% CI: 1.29-3.84), and p-value of 0.003 suggests a statistically significant association of hypovitaminosis D with preeclampsia.

Conclusion: There was observed to be a significant association between low levels of vitamin D and the development of pre-eclampsia in the later stages of pregnancy. Women with pre-eclampsia are more likely to have a deficiency in vitamin D compared to women with normal blood pressure.

Keywords: Pre-eclampsia, third trimester, Vitamin D, Hypovitaminosis.

Cite this article as: Mustafa R, Khan B, Syed SZ, Iqbal Quereshi MA, Kousar S, Zafar I. Correlation Between Low Vitamin D Levels and Pre-eclampsia Onset in Late Pregnancy. J Soc Obstet Gynaecol Pak. 2023; 13(4):403-407.

Introduction

Pre-eclampsia, a hypertensive disorder specific to pregnancy, poses significant risks to both maternal and fetal health. The etiology of pre-eclampsia remains complex and multifactorial, with various genetic, immunological, and environmental factors implicated. Among these factors, the role of vitamin D status has garnered attention due to its potential influence on vascular function and immune regulation.

Pre-eclampsia (PE) stands as one of the prevailing pregnancy disorders, typically emerging after the 20th week of gestation. It manifests through symptoms such as elevated blood pressure, protein in the urine (proteinuria), and indications of organ impairment.[1]

Globally, PE impacts approximately 2% to 8% of pregnancies and carries enduring ramifications for maternal health, extending to cerebrovascular diseases,

Authorship Contribution: [1,2]Substantial contributions to the conception or design of the work or the acquisition, Final approval of the version to be published. [3,4,6] Drafting the work or revising it critically for important intellectual content, [5]Active participation in methodology.

Funding Source: none
Conflict of Interest: none

Received: March 09, 2023
Accepted: Sept 30, 2023

metabolic syndrome, and cardiovascular complications.[1,2] It affects 2–8% of pregnancies and is responsible for 25% of maternal mortality, as well as fetal complications and mortality.[3] The exact cause of preeclampsia remains unclear, and there is currently no effective preventive treatment. Various factors, including genetic predisposition, abnormalities in placental development, inflammation, oxidative stress, and immune system dysregulation, contribute to endothelial dysfunction, which is central to the development of preeclampsia.[4]

The inadequate levels of vitamin D in the women during pregnancy, alongside numerous other deficiencies that commonly occur during pregnancy, pose a significant public health concern.[5,6] Insufficient vitamin D concentrations during gestation have been linked with various adverse consequences, including gestational diabetes, pre-eclampsia, and impaired fetal skeletal development. Calcium metabolism disorders, such as hyporcalciuria and low levels of vitamin D, have consistently been observed during the pregnancy of women who subsequently develop preeclampsia.[7,8] The involvement of vitamin D in pre-eclampsia is linked to its impact on the renin-angiotensin system (RAS). Vitamin D serves as a negative regulator of the RAS, inhibiting the expression of the renin gene. Consequently, serum levels of vitamin D are inversely correlated with blood pressure and renin activity. However, pre-eclampsia is believed to have its origin in early pregnancy, characterized by the maternal immune system restricting placental invasion in mothers susceptible to cardiovascular diseases.[9] During pregnancy, vitamin D is believed to contribute to implantation and placental function, possibly because of its angiogenic, immunomodulatory, and anti-inflammatory properties.[9]

Based on a comprehensive systemic analysis of worldwide mortality, Pakistan ranks as the sixth most populous country and carries the 3rd higher burden of the mortality of fetus, mother and the child.[10] Within developing nations, pre-eclampsia stands out as a significant contributor to maternal mortality, accounting for a substantial portion, ranging from 40% to 60%, of maternal deaths.[11] This condition, characterized by hypertension and often proteinuria during pregnancy, poses a considerable health risk to expectant mothers in regions where access to adequate prenatal care and medical interventions may be limited. There is a lack of exact data in Pakistan regarding the incidence of insufficient vitamin D levels among females with pre-eclampsia. However, few recent studies have shown conflicting findings; for instance, one study observed the higher rate of 82.8% of vitamin D deficiency in pre-eclamptic women,[12] while another found that 60.0%.[13]

Given the increased rate insufficient level of the vitamin D among females with pre-eclampsia and the inconsistent results from previous research, this study aims to investigate the current situation. By doing so, it seeks to explore recent information that may be helpful in the development of strategies aimed at reducing morbidity and mortality associated with pre-eclampsia.

Methodology

This observational case control study was carried out at department of Obstetrics and Gynaecology, Lady Willingdon Hospital (LWH), Lahore. Study was done during a period of six months from June 2021 to 31 December 2021. Non probability consecutive sampling technique was used. All the women aged 18 years or older, gestational age more than 28 weeks, diagnosed with pre-eclampsia as per established clinical criteria were included. Women with first and second trimesters of pregnancy, women with pre-existing conditions known to affect vitamin D metabolism or pre-eclampsia, women on vitamin D supplementation and those who were not agreeing to participate in the study were excluded. In this case-control study, an investigation was conducted to explore the correlation between low vitamin D levels and the onset of pre-eclampsia in late pregnancy. Equal numbers of normotensive women were selected as controls after obtaining their written informed consent and explaining the purpose and objectives of the study.

A 5ml blood sample was collected from each participant, and promptly sent to the Hospital diagnostic laboratory for analysis. Pre-eclampsia was defined as the onset of hypertension (blood pressure ≥ 140/90 mmHg) after 20 weeks of gestation accompanied by proteinuria (≥ 300 mg/24 hours or a dipstick reading of ≥ 2+). Vitamin D deficiency was defined as serum levels below 20 ng/mL.

The economic burden associated with vitamin investigation was assumed by the researcher. All the information regarding data was collected using study proforma and SPSS version 26 was used for the data analysis.

Results

Based on the demographic characteristics of 330 participants, split into case and control groups, the average age for the case group was 27.22 ± 3.18 years, and for the control group, it was 26.31 ± 4.17 years.

Table I: Descriptive statistics of demographic characteristics. (n=330)

Variables		Study groups		p-value
		Case group	Control group	
Age	**Mean±SD**	27.22±3.18 years	26.31±4.17 years	0.780
Gestational age	**Mean±SD**	32.38±3.5 weeks	33.29±2.7 weeks	0.811
Parity	**Primiparous**	34	33	0.603
		20.6%	20.0%	
	Prity -I	39	40	
		23.6%	24.2%	
	Parity-II	49	40	
		29.7%	24.2%	
	Parity-III	18	27	
		10.9%	16.4%	
	Parity- IV	25	25	
		15.2%	15.2%	
Total		165	165	
		100.0%	100.0%	

Table II: Comparison of hypovitaminosis D with study groups. (n=330)

Variables		Study Groups		Total	OR [95% CI]
		Case	Control		
Hypovitaminosis D	**Yes**	47	25	72	2.23 [1.29-3.84]
		28.5%	15.2%	21.8%	
	No	118	140	258	
		71.5%	84.8%	78.2%	
Total		165	165	330	
		100.0%	100.0%	100.0%	
Chi value=8.59, (p-value=0.003)*					

Table III: Comparison of hypovitaminosis D in groups according to age and parity. (n=330)

Variables		Vitamin D Deficiency	Study Groups		Total	OR [95% CI]	p-value
			Case	Control			
Age groups	**≤ 30**	**Yes**	38	16	**54**	2.615 [1.364-5.013]	0.003*
		No	89	98	**187**		
	> 30	**Yes**	9	9	**18**	1.448 [0.513-4.090]	0.483
		No	29	42	**71**		
Parity	Primiparous	Yes	20	9	29	2.683 [1.128-6.385]	0.023*
		No	53	64	117		
	Multiple	Yes	27	16	43	1.973 [0.978-3.979]	0.055
		No	65	76	141		

*Chi value=8.59, (p-value=0.003)**

Similarly, the mean gestational age for the case group was 32.38 ± 3.5 weeks, and for the control group, it was 33.29 ± 2.7 weeks, with a significant p-value of p > 0.05. Parity data is presented as frequencies and percentages for each parity level within both case and control groups, indicating a non-significant difference in parity distribution between the groups (p-value 0.603), as shown in Table I.

In the case group, 47 individuals (28.5%) were found to have hypovitaminosis D, while in the control group, 25 individuals (15.2%) were identified with the condition. The odds ratio (OR) for hypovitaminosis D between the case and control groups was calculated as 2.23 (95% CI: 1.29-3.84), indicating a higher likelihood of hypovitaminosis D among the case group compared to the control group. The p-value of 0.003 suggests a statistically significant association of hypovitaminosis D with preeclampsia. (Table II)

Furthermore, the incidence of hypovitaminosis D was statistically significant according to age of the women and parity (p-<0.05), as shown in table III and IV.

Discussion

Preeclampsia, a potentially serious pregnancy complication marked by elevated blood pressure and often linked with protein in the urine, presents substantial threats to the health of both the mother and the fetus. Recent research has placed greater emphasis on comprehending the impact of vitamin D during pregnancy. Maintaining sufficient levels of vitamin D at

this stage could potentially diminish the likelihood of preeclampsia by supporting healthy placental function and lessening inflammation. The current study investigated 165 women with preeclampsia alongside an equal number of normotensive pregnant women to assess the association between low vitamin D levels and the onset of pre-eclampsia during the third trimester of pregnancy. Demographically, the average age in the case group was 27.22 ± 3.18 years, and in the control group, it was 26.31 ± 4.17 years. The mean gestational age was 32.38 ± 3.5 weeks in the case group and 33.29 ± 2.7 weeks in the control group. Parity data revealed no significant difference between the groups (p-value 0.603). Comparatively, Rafiq et al.[14] reported an average patient age of 27.48 years, with a standard deviation of 5.618 years, and a mean gestational age of 35.05 weeks, with a standard deviation of 2.9554 weeks. Similarly, Shen et al.[15] found an average recruitment age of 30.3 years, with a standard deviation of 5.0 years, and a median gestational age at delivery of 39.4 weeks.

Additionally, Tabassum et al.[16] noted that the average age of women with preeclampsia was 25.44 years, with a standard deviation of 4.77 years, ranging from 20 to 38 years, and the mean gestational age at the onset of pre-eclampsia was 33.12 weeks, with a standard deviation of 2.54 weeks.

In this study in the case group, 47 individuals (28.5%) were found to have hypovitaminosis D, while in the control group, 25 individuals (15.2%) were identified with the condition. The odds ratio (OR) and p-value of 0.003 suggests a statistically significant association of hypovitaminosis D with preeclampsia. Consistently Arumaikannu J et al[4] reported that the prevalence of vitamin D deficiency was 69%, with around 37% of women diagnosed with preeclampsia and 32% of normotensive women showing vitamin D levels below 20ng/ml. In another study by Singh A et al[12] reported that out 159(82.8%) patients with preeclampsia were found to have Vitamin D deficiency, while 33 (17.2%) were deemed to have sufficient levels of the vitamin.

Similarly, Nandedkar AM et al[17] conducted a case-control study to examine vitamin deficiency in women with preeclampsia, reporting that 95% of cases had lower levels of vitamin D (35% insufficiency and 60% deficiency) compared to 72% (46% insufficiency and 28% deficiency) in the control group. In the comparison of this series the Singla R et al.[18] carried out a study that compared the average vitamin D levels in women with preeclampsia and those without. Their research uncovered a significant link between vitamin D deficiency and preeclampsia. The findings suggested that preeclamptic women tended to have lower serum concentrations, indicating a potential involvement of vitamin D deficiency in the development of the disease.[18] Several other studies have also shown a strong link between vitamin D deficiency and pre-eclampsia.[19,20] However, the mechanisms connecting vitamin D deficiency to the onset of pre-eclampsia are not exactly known. Some proposed mechanisms include the vital role of vitamin D in immune regulation, inflammation, and vascular function, all of which are involved in the development of pre-eclampsia.[21]

Additionally, the presence of vitamin D receptors in the placenta suggests its significance in placental development and function. Therefore, vitamin D deficiency may disrupt these processes, ultimately raising the risk of pre-eclampsia. Additionally, deficiency in vitamin D has been linked to endothelial dysfunction and impaired vascular remodeling,[22] both of which are key characteristics of pre-eclampsia. Endothelial dysfunction can lead to vasoconstriction, inflammation, and oxidative stress, ultimately contributing to the development of hypertension and proteinuria, both of which are characteristic of pre-eclampsia. [23,24] These findings have significant implications for clinical practice.

Recognizing and addressing vitamin D deficiency in pregnant women, especially those at high risk for pre-eclampsia, could have important implications for the prevention and management of this condition. Strategies such as vitamin D supplementation or increased exposure to sunlight may help reduce the risk of pre-eclampsia in the susceptible individuals.

Conclusion

Based on study conclusion, it is evident that there is a connection between low levels of vitamin D and the development of pre-eclampsia in the later stages of pregnancy. Women with pre-eclampsia are more likely to have a deficiency in vitamin D compared to women with normal blood pressure. Further investigation is needed to understand the underlying mechanisms and potential benefits of vitamin D supplementation for preventing and managing pre-eclampsia.

References

1. Al Subai A, Baqai MH, Agha H, Shankarlal N, Javaid SS, Jesrani EK, Golani S, Akram A, Qureshi F, Ahmed S, Saran S. Vitamin D and preeclampsia: A systematic review and meta-analysis. SAGE Open Medicine. 2023;11:20503121231212093.

2. Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007; 335(7627): 974.
3. Behjat Sasan S, Zandvakili F, Soufizadeh N, Baybordi E. The effects of vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia. Int. J. Gynecol. Obstet. 2017 Oct;2017.
4. Arumaikannu J, Rani SU, Shanthi S. Role of vitamin D in preeclampsia: Our experience. Int J Clin Obstet Gynaecol. 2018;2:29-32.
5. Dahma G, Neamtu R, Nitu R, Gluhovschi A, Bratosin F, Grigoras ML, Silaghi C, Citu C, Orlu IN, Bhattarai S, Mocanu AG. The influence of maternal vitamin D supplementation in pregnancies associated with preeclampsia: a case-control study. Nutrients. 2022 Jul 22;14(15):3008.
6. Citu IM, Citu C, Margan MM, Craina M, Neamtu R, Gorun OM, et al. Calcium, magnesium, and zinc supplementation during pregnancy: The additive value of micronutrients on maternal immune response after SARS-CoV-2 infection. Nutrients. 2022 Mar 30;14(7):1445.
7. Behjat Sasan S, Zandvakili F, Soufizadeh N, Baybordi E. The effects of vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia. Int. J. Gynecol. Obstet. 2017 Oct;2017.
8. Steegers E. A., von Dadelszen P., Duvekot J. J., Pijnenborg R. Pre-eclampsia. *The Lancet.* 2010;376(9741):631–644.
9. Karpa M, Thakur S, Singh K, Sharma J, Chaudhary H. To compare serum Vitamin D status in pre-eclamptic and non-preeclamptic pregnant women in labour: A tertiary care centre study of Northern India. Clin. Gynecol. Obstet. 2022 Jan 28;5(1):013-8.
10. Soomro S, Kumar R, Lakhan H, Shaukat F. Risk factors for pre-eclampsia and eclampsia disorders in tertiary care center in Sukkur, Pakistan. Cureus. 2019 Nov 10;11(11).
11. Birhanu MY, Temesgen H, Demeke G, Assemie MA, Alamneh AA, Desta M, Toru M, Ketema DB, Leshargie CT. Incidence and predictors of pre-eclampsia among pregnant women attending antenatal care at debre markos referral hospital, north west ethiopia: Prospective cohort study. Int. J. Women's Health7. 2020 Nov 10:1013-21.
12. Singh A, Mishra S, Aditya V, Srivastava R. Association of vitamin D deficiency with occurrence of pre eclampsia among inpatients of tertiary care centre, Gorakhpur, Uttar Pradesh, India. Int. j. reprod. contracept. 2016 May 1;5(5):1304-9.
13. Aziz H, Abrar F, Gul S, Masud A, Awan SN, Qamar S. Association of Vitamin D 25 (OH) D Deficiency as a Risk Factor for Pre-Eclampsia. PJPH. 2021 Oct 25;11(3):178-83.
14. Rafiq S, Khan AB, Bibi U, Bibi N, Parveen Z. Fetal Outcome in Patients with Pre-Eclampsia at Ayub Teaching Hospital Abbottabad. Pakistan Journal of Medical & Health Sciences. 2022;16(12):181.
15. Shen M, Smith GN, Rodger M, White RR, Walker MC, Wen SW. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PloS one. 2017 Apr 24;12(4):e0175914.
16. Tabassum S, Mumtaz S, Fayyaz A, Suman F, Qadir SY. Frequency of pre-ec-lampsia in patients with abnormal uterine artery Doppler at twenty two to twenty four weeks of gestation. Professional Med J 2020; 27(6):1280-1284
17. Nandedkar AM, Bachewar P, Memon M. Prevalence of vitamin D3 deficiency and its correlation with high-risk pregnancy pre-eclampsia and eclampsia study from central India. Int J Reprod Contracept Obstet Gynecol .2022;12(1):186.
18. Singla R, Gurung P, Aggarwal N, Dutta U, Kochhar R. Relationship between preeclampsia and vitamin D deficiency: a case control study. Arch. Gynecol. Obstet. 2015 Jun;291:1247-51.
19. Gad Alrb MT, Hassan MM, Bahaa El-Den HA, Ali AM. Vitamin D Level in Patients Suffering from Pregnancy Induced Hypertension. Minia Journal of Medical Research. 2019;1;30(3):42-5.
20. Hina U, Choudry A, Saeed S, Khanam F, Urooj U. Association of Low Vitamin D Level Status and Risk of Pre-Eclampsia and Preterm Birth in Women Using Low-Dose Aspirin. PAFJM. 2022 Nov 10;72(5):1576-80.
21. Purswani JM, Gala P, Dwarkanath P, Larkin HM, Kurpad A, Mehta S. The role of vitamin D in pre-eclampsia: a systematic review. BMC pregnancy and childbirth. 2017 Dec;17:1-5.
22. Sen A, Vincent V, Thakkar H, Abraham R, Ramakrishnan L. Beneficial role of vitamin D on endothelial progenitor cells (EPCs) in cardiovascular diseases. Journal of Lipid and Atherosclerosis. 2022 Sep;11(3):229.
23. Mannaerts D, Faes E, Gielis J, Van Craenenbroeck E, Cos P, Spaanderman M, Gyselaers W, et al. Oxidative stress and endothelial function in normal pregnancy versus pre-eclampsia, a combined longitudinal and case control study. BMC pregnancy and childbirth. 2018 Dec;18:1-9.
24. McElwain CJ, Tuboly E, McCarthy CM. Mechanisms of endothelial dysfunction in pre-eclampsia and gestational diabetes mellitus: windows into future cardiometabolic health? Frontiers in endocrinology. 2020 Sep 11;11:569593.